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21874	7590	11/06/2006	EXAMINER	
EDWARDS & ANGELL, LLP P.O. BOX 55874 BOSTON, MA 02205			SHAW, AMANDA MARIE	
			ART UNIT	PAPER NUMBER
			1634	

DATE MAILED: 11/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No. 10/714,470	Applicant(s) DIETZ ET AL.	
	Examiner Amanda M. Shaw	Art Unit 1634	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☐ Responsive to communication(s) filed on 06 October 2006.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1 and 3-15 is/are pending in the application.
- 4a) Of the above claim(s) 14 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1, 3-13, and 15 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

1. This action is in response to the amendment filed October 6, 2006. Applicant's arguments have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. This action is made final.

Claims 1, 3-15 are currently pending. Claims 14 has been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Claims 1, 6, and 13 have been amended. Claim 15 is newly presented. Therefore Claims 1, 3-13, and 15 will be addressed herein.

#### ***Information Disclosure Statement***

2. The present application lacks an information disclosure statement (IDS). Information disclosure statements are not required however if the applicant wants the references listed in the specification at pages 21-24 considered they must be submitted on an IDS form.

#### ***Claim Rejections - 35 USC § 112***

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

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art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-13 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons set forth in the office action of July 12, 2006 and reiterated below. This is a Written Description rejection.

The claims are drawn broadly to encompass methods for treating a patient suffering of susceptible to coronary artery disease comprising selecting a patient that has the KL-VS allele and treating the selected patient by administering a therapeutic agent for coronary artery disease. Accordingly, the claims encompass any known therapeutic agent.

The specification at page 6 teaches that therapeutic agents such as nitrate may be administered to the selected patient which has the KL-VS allele. While methods for treating the selected patient with nitrate meet the written description requirements of 35 U.S.C. 112, first paragraph, the specification does not disclose and fully characterize methods for treating the selected patient by administering any therapeutic drug.

*Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, clearly states that 'applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable

from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that 'An adequate written description of a DNA...requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the specification only teaches the use of nitrate to treat individuals with the KL-VS allele. The disclosure of one type of treatment is not representative of the entire genus of therapeutic agents to treat coronary artery disease. It is then determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g. restriction map, biological activity of an encoded protein product, etc.). In the instant case, no such identifying characteristics have been provided. Yet, the claims as written are inclusive of a potentially large genus of therapeutic treatments for coronary artery disease. Conception of the claimed invention cannot be achieved until reduction to practice has occurred, regardless of the complexity or simplicity of potential methods

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for isolating additional nucleotide variations. As stated in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. LTD*, 25 USPQ2d 1016, one cannot describe what one has not conceived.

For these reasons, Applicants have not provided sufficient evidence that they were in possession, at the time of filing, of the invention as it is broadly claimed and thus the written description requirement has not been satisfied for the claims as they are broadly written. Applicants attention is drawn to the Guidelines for the Examination of Patent Applications under 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

#### **RESPONSE TO ARGUMENTS**

4. In the response filed October 6, 2006, Applicants traversed this rejection by stating that the claims are not drawn to methods for treating the selected patient by administering any therapy or therapeutic agent. Applicants state that the instant claims specify that the therapeutic agent or therapy is "for coronary artery disease". This argument has been fully considered but is not persuasive because claims 10-13 still do not teach a representative number of therapeutic agents for coronary artery disease, a representative number of surgeries for coronary artery disease, or a representative number of lifestyle changes for treatment for coronary artery disease. It is noted that the specification on page 6 teaches "that the invention includes methods for treating a patient suffering or susceptible to coronary artery disease. Such methods include identifying and selecting a patient that is need of treatment, particularly a patient that

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has a KL-VS allele as may be determined by techniques disclosed herein. The selected patient is then treated for coronary artery disease. For example an effective amount and regime of a therapeutic agent may be administered to the selected patient, such as a nitrate (e.g. nitroglycerine as may be suitably administered sublingually, or an amyl nitrate, isosorbide dinitrate or pentaerythritol tetranitrate); lifestyle change such as to eliminate or reduce smoking, weight loss, increase or aerobic exercise and the like; or surgical intervention such as coronary arterial bypass surgery". However there are additional therapeutic agents, lifestyle changes, and surgeries that can be used to treat coronary artery disease. For example the National Heart Lung and Blood Institute suggests the following lifestyle changes: eating healthy to reduce high blood pressure and high cholesterol and to maintain a healthy weight, quitting smoking, exercising, losing weight if you are obese, and reducing stress to treat coronary artery disease. Thus the disclosure of three types of lifestyle changes is not representative of the entire genus of lifestyle changes that can be made to treat coronary artery disease. The National Heart Lung and Blood Institute also suggests the following therapeutic agents: cholesterol lowering medicines, anticoagulants, aspirin, ACE, beta blockers, calcium channel blockers, nitroglycerin, long acting nitrates, glycoprotein inhibitors, and thrombolytic agents to treat coronary artery disease. Thus the disclosure of one type of therapeutic agents is not representative of the entire genus of therapeutic agents that are used to treat coronary artery disease. The National Heart Lung and Blood Institute also suggest the following surgical procedures: angioplasty and coronary artery bypass

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surgery to treat coronary artery disease. Thus the disclosure of one type of surgery is not representative of the entire genus of surgeries used to treat coronary artery disease.

***Claim Rejections - 35 USC § 102***

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-3, 5, and remain rejected under 35 U.S.C. 102(a) as being anticipated by Arking et al (PNAS Published 1/02) for the reasons set fourth in the Office Action of 7/12/2006 and reiterated below.

Regarding Claim 1, Arking et al teach a method comprising isolating DNA from a patient and analyzing the DNA to detect the presence of the KL-VS allele. Specifically Arking teach that the KL-VS variation in the klotho gene contributes to the onset and severity of human age related phenotypes. Arking et al teach that common age related phenotypes include atherosclerosis, osteoporosis, emphysema and infertility (Abstract and Page 856). Atherosclerosis is a condition that occurs when arteries become narrow and hardened due to cholesterol plaque buildup and causes coronary artery disease. Therefore since the presence of the KL-VS allele is linked to atherosclerosis, the presence of the KL-VS allele also indicates the patient is predisposed to develop coronary artery disease.



Regarding Claim 3 Arking et al teach the digestion of the klotho gene using Mae III (858). The reference does not exemplify the size of the restriction fragment however the restriction fragments of 265 and 185 base pairs are considered an inherent property of the KL-VS allele since Mae III cuts DNA at GTNAC.

Regarding Claim 5 Arking et al teach a method further comprising a step of amplifying the nucleic acid. Specifically Arking et al teach that exons 1-5 of the klotho gene were analyzed by single-strand conformation polymorphism (SSCP) analysis. Prior to SSCP analysis exon 1 was amplified using the Advantage-GC Genomic PCR kit (CLONTECH) and exons 2-5 were amplified using AmpliTaq Gold (Perkin-Elmer).

Regarding Claim 9 Arking et al teach a method comprising: detecting in a patient the presence of at least one copy of the KL-VS allele. Specifically Arking teach that DNA was isolated from the subjects and used for SSCP analysis and DNA sequencing to detect the KL-VS allele (Page 857). Additionally Arking et al teach that the KL-VS variation in the klotho gene contributes to the onset and severity of human age related phenotypes. Arking et al teach that common age related phenotypes include atherosclerosis, osteoporosis, emphysema and infertility (Abstract and Page 856). Atherosclerosis is a condition that occurs when arteries become narrow and hardened due to cholesterol plaque buildup and causes coronary artery disease. Therefore since the presence of the KL-VS allele is linked to atherosclerosis the presence of the KL-VS allele also indicates the patient has increased propensity for coronary artery disease.

## RESPONSE TO ARGUMENTS

6. In the response filed October 6, 2006, Applicants traversed the rejection over Arking by stating that Arking et al do not address all of the limitations set forth in claim 1. Specifically the Applicants state that Arking et al do not teach a method for determining predisposition to coronary artery disease because Arking et al do not teach an association between the KL-VS allele with coronary artery disease. This argument has been fully considered but is not persuasive because Arking et al do in fact teach an association between the KL-VS variation and coronary artery disease. Specifically Arking et al teaches that the KL-VS variation in the klotho gene contributes to the onset and severity of human age related phenotypes. Arking et al teach that common age related phenotypes include atherosclerosis, osteoporosis, emphysema and infertility (Abstract and Page 856). The National Heart Lung and Blood Institute teach that "Coronary artery disease (CAD) occurs when the arteries that supply blood to the heart muscle (the coronary arteries) become hardened and narrowed. The arteries harden and narrow due to buildup of a material called plaque on their inner walls. The buildup of plaque is known as atherosclerosis". Therefore since the presence of the KL-VS allele is linked to atherosclerosis, and atherosclerosis causes CAD it would be obvious that the presence of the KL-VS allele could be used to indicate ones predisposition to develop coronary artery disease.

***Claim Rejections - 35 USC § 103***

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 4, 6 –7 remain rejected and newly presented Claim15 is also rejected under 35 U.S.C. 103(a) as being unpatentable over Arking et al (PNAS published 1/02) in view of Francis et al (US Patent 6210877 Issued 3/01) for the reasons set forth in the Office Action of 7/12/2006 and reiterated below.

The teachings of Arking et al are presented above in paragraph 6.

Regarding Claims 4 and 6 Arking et al teach a method comprising amplification and SSCP analysis in order to identify patients which have the KL-VS allele.

Arking et al do not teach a method wherein the KL-VS allele is detected by RFLP analysis wherein the analysis comprises (i) amplifying the DNA in a polymerase chain reaction to produce an amplification product; (ii) treating the amplified DNA with one or more restriction fragment enzymes; and (iii) size fractionation of the amplification products.

However Francis et al teach a method for predicting a patient's risk for coronary artery disease by detecting the presence or absence of a particular allele linked with

coronary artery disease. Francis et al teach that restriction fragment length polymorphism (RFLP) may be used for detecting the presence of a particular marker. RFLP is a method in which DNA is cut into restriction fragments by restriction endonucleases. The restriction fragments are then separated according to length by gel electrophoresis. Francis et al further teach that RFLP may also comprise the step of amplifying the nucleic acid before cutting the DNA. (Abstract and Column 6).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Arking et al so as to have used RFLP analysis as suggested by Francis et al because RFLP is an equally effective means for detecting the presence/absence of an allele.

Regarding Claim 7 Arking et al teach a method comprising amplification and SSCP analysis in order to identify patients which have the KL-VS allele.

Arking et al do not exemplify a method in which the amplification is performed with one or more oligonucleotides selected from the group consisting of: sense primer 5' AGGCTCATGCCAAAGTCTGG 3' (SEQ ID No: 5); and antisense primer 5' GTTCCATGATGAACTTTTGAGG 3' (SEQ ID No: 6).

However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use SEQ ID NO: 6 to amplify the nucleic acid because the inverse complement of SEQ ID NO: 6 flanks the region where the KL-VS allele is present (SEQ ID NO 6 aligns with nucleic acids 1307-1320 of Accession Number 24497613). The amplification of a target region using primers was well known in the art at the time the invention. Designing primers which are equivalents to those taught in

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the art is routine experimentation. The parameters and objectives involved in the selection of primers were well known in the art at the time the invention was made. Moreover, software programs were readily available which aid in the identification of conserved and variable sequences and in the selection of optimum primer pairs. The prior art is replete with guidance and information necessary to permit the ordinary artisan to design primers for the amplification of klotho intron and exon sequences. The ordinary artisan would have been motivated to have designed additional primers for amplifying klotho so as to have provided primers which would amplify and allow for the detection of the KL-VS allele. Further, the ordinary artisan would have had more than a reasonable expectation of success of obtaining additional primers for amplifying klotho sequences. Thus, for the reasons provided above, a method using the primer of SEQ ID NO: 6 would have been obvious to one of ordinary skill in the art.

THE FOLLOWING IS A NEW GROUND OF REJECTION NECESSITATED BY  
APPLICANTS AMENDMENTS TO THE CLAIMS:

Regarding Claim 15 Arking et al do not teach that the method further comprises the step of comparing the presence or absence of the KL-VS allele in the patient to a control.

However Francis et al teach a method where nucleic acid from a patient is compared to a control. Preferably the control sample contains alleles that are known to be associated with coronary artery disease. Similarity of the identified alleles from the

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patient to the control sample indicates the patient's predisposition to coronary artery disease (Column 4).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Arking et al by adding a step of comparing the presence or absence of the KL-VS allele in the patient to a control as suggested by Francis et al because comparing a test sample to a control sample and detecting sequence differences was routinely performed in the art as demonstrated by Francis et al.

8. Claim 8 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Arking et al (PNAS published 1/02) in view of Francis et al (US Patent 6210877 Issued 3/01) and in further view of Levitt (US Patent 5908839 Issued 6/99) for the reasons set forth in the Office Action of 7/12/2006 and reiterated below.

The teachings of Arking et al and Francis et al are presented above in paragraphs 6 and 7.

Regarding Claim 8 the combined references do not teach that the oligonucleotide primers are detectably labeled.

However Levitt et al teach a method which utilizes labeled primers to amplify DNA prior to RFLP analysis. Specifically Levitt et al teach that to test for the presence of a DNA sequence variant a primer was end labeled prior to PCR amplification. The PCR product was then digested with StyI producing two fragments 108 bp [labeled] and 52 bp [unlabeled] in length (Column 22)

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Arking et al so as to have used primers with detectable labels in order to have achieved the benefits set forth by Levitt et al of providing a method in which a detectable label is used in order to further confirm the presence of a polymorphism.

9. Claims 10-13 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Arking et al (PNAS published 1/02) in view of Bockow et al (US 2002/0055539 Filed 3/01) for the reasons set forth in the Office Action of 7/12/2006 and reiterated below.

The teachings of Arking et al are presented above in paragraph 6.

Regarding Claims 10-13 Arking et al teach a method comprising identifying patients which have the KL-VS allele.

Arking et al does not teach a method further comprising treating the patient for coronary artery disease by (i) administering a therapeutic agent; (ii) surgery; or (iii) a lifestyle change.

However Bockow et al teach compositions and methods for treating or preventing cardiovascular conditions such as coronary artery disease. Specifically Bockow et al teach that the intravascular administration of omega fatty acids can be used to treat or prevent cardiovascular conditions. In the instant case this is being interpreted as administering a therapeutic agent. Bockow et al also teach that bypass surgery with

synthetic or vein grafts is a standard surgical approach to treat cardiovascular conditions. Additionally Bockow et al teach that another current treatment for cardiovascular conditions is directed to reducing risk factors such as reduction of cholesterol, smoking avoidance, normalizing blood pressure, decreasing weight and increasing exercise. In the instant case these are being interpreted as lifestyle changes.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Arking et al so as to have further provided a treatment in order to have achieved the benefits set forth by Bockow et al of providing methods which reduce the morbidity and mortality caused by cardiovascular conditions such as coronary artery disease.

### **RESPONSE TO ARGUMENTS**

10. In the response filed October 6, 2006, Applicants traversed the rejection over Arking in view of Francis, Levitt, and Bockow by stating that Arking et al do not address all of the limitations set forth in claim 1. Specifically the Applicants state that Arking et al do not teach a method for determining predisposition to coronary artery disease because Arking et al do not teach an association with the presence of the KL-VS allele with coronary artery disease. The applicants also state that the teachings of Francis, Levitt, and Bockow et al do not cure the defects of Arking. This argument has been fully considered but is not persuasive because Arking et al do in fact teach an association between the KL-VS variation and coronary artery disease. Specifically Arking et al teaches that the KL-VS variation in the klotho gene contributes to the onset and severity



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of human age related phenotypes. Arking et al teach that common age related phenotypes include atherosclerosis, osteoporosis, emphysema and infertility (Abstract and Page 856). The National Heart Lung and Blood Institute teach that "Coronary artery disease (CAD) occurs when the arteries that supply blood to the heart muscle (the coronary arteries) become hardened and narrowed. The arteries harden and narrow due to buildup of a material called plaque on their inner walls. The buildup of plaque is known as atherosclerosis". Therefore since the presence of the KL-VS allele is linked to atherosclerosis, and atherosclerosis caused CAD it would be obvious that the presence of the KL-VS allele could be used to indicate one's predisposition to develop coronary artery disease.

### ***Conclusion***


11. No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Amanda M. Shaw  
Examiner  
Art Unit 1634

  
A handwritten signature in black ink, appearing to read 'R. Shukla', is written over a long, slightly curved horizontal line.

**RAM R. SHUKLA, PH.D.  
SUPERVISORY PATENT EXAMINER**